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Droperidol for Agitation in Acute Care

Rapid Review

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Abbreviations

AAEM	American Academy of Emergency Medicine
AMSS	Altered Mental Status Scale
BARS	Behavioural Activity Rating Scale
COI	conflict of interest
ECG	electrocardiogram
ED	emergency department
EPS	extrapyramidal symptoms
$ETCO_2$	end-tidal carbon dioxide
IM	intramuscular
LOS	length of stay
MA	meta-analysis
PICO	population, intervention, comparator, outcome
PICU	psychiatric intensive care unit
QTc	corrected QT interval
RCT	randomized controlled trial
RR	relative risk
SpO_2	peripheral oxygen saturation
SR	systematic review

Key Messages

- Comparative evidence supports that droperidol is as effective as haloperidol and olanzapine for the sedation of adult patients with uncontrolled aggression, anxiety, or violent behaviour in acute care settings, and a limited quantity of evidence supports the superiority of droperidol over ziprasidone and lorazepam monotherapies.
- There are no statistically significant differences in adverse event frequency or severity in adult patients treated with droperidol compared with haloperidol or olanzapine.
- Guidelines published in 2015 support the safety and efficacy of droperidol treatment for agitation based on high-quality relevant evidence.
- These guidelines found insufficient evidence to support electrocardiogram or telemetry monitoring of patients who were administered less than 2.5 mg of droperidol.

Context and Policy Issues

Agitation, aggression, and violent behaviour commonly present in acute care settings and may be a factor in up to 2.6% of emergency department (ED) encounters in the US.[1,2] Agitation is often of unknown or multifactorial etiology; however, it is commonly a result of alcohol or drug intoxication, trauma, or mental health disorders.[3,4] Patients with agitation can present a risk to staff, other patients, and property. Therefore, for cases in which verbal de-escalation fails, physical restraint and sedation may be required to ensure a safe environment where further acute care diagnosis and treatment can proceed.[5,6] Treatment goals for this indication are rapid and safe sedation.[6]

Droperidol is a butyrophenone used in acute care settings for a variety of purposes, including the rapid sedation of patients with agitation, aggression, or who are exhibiting violent behaviour.[4,7] Droperidol can be administered intravenously and it can also be administered intramuscularly, which has practical advantages when safely dealing with agitated patients.[7] Many antipsychotic drugs, including droperidol, haloperidol, and olanzapine, have a similar adverse event profile that includes serious events such as respiratory depression, cardiac events, and extrapyramidal symptoms (EPS).[4]

In 2001, a black box warning was issued by the US FDA for the use of droperidol based on post-marketing surveillance data.[3,7] The black box warning emphasized careful patient selection and increased monitoring to prevent corrected QT (QTc) interval elongation in patients administered droperidol.[7] QTc elongation can lead to sudden cardiac death. The extra burden placed on management of patients with droperidol has greatly decreased its use and availability in the US.[7]

The purpose of this report was to retrieve and review the current evidence on the safety and efficacy of droperidol for patients with agitation, aggression, or violent behaviour in acute care settings. In addition, this report aimed to retrieve and review relevant evidence-based guidelines regarding the use of droperidol in acute care settings.

Research Questions

1. What is the clinical effectiveness of droperidol for the management of violence and aggression in acute care settings?
2. What are the evidence-based guidelines regarding the use of droperidol in acute care settings?

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including MEDLINE and Embase via OVID, the Cochrane Database of Systematic Reviews, the international HTA database, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were *droperidol* and *acute care* or *agitation*. No search filters were applied to limit retrieval to study type. Comments, newspaper articles, editorials, letters, and conference abstracts were excluded. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2010, and December 9, 2020.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, were duplicate publications, or were published before 2010. Systematic reviews (SRs) in which all relevant studies were captured in other more recent or more comprehensive SRs were

Table 1: Selection Criteria

Criteria	Description
Population	Adult patients in acute care settings
Intervention	Droperidol
Comparator	Standard care (i.e., other antipsychotic drugs, such as haloperidol or olanzapine)
Outcomes	Research Question 1: Effectiveness (e.g., treatment agitation, aggression, violence) and safety Research Question 2: Recommendations regarding patient monitoring
Study designs	Health technology assessments, systematic reviews, randomized controlled trials, observational comparative studies, and evidence-based guidelines

excluded. Primary studies retrieved by the search were excluded if they were captured in 1 or more included SRs. Guidelines with unclear methodology were also excluded.

Critical Appraisal of Individual Studies

The included publications were critically appraised by 1 reviewer using the following tools as a guide: A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2)[8] for SRs, the Downs and Black checklist[9] for randomized and non-randomized studies, and the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument[10] for guidelines. Summary scores were not calculated for the included studies; rather, the strengths and limitations of each included publication were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 375 citations were identified in the literature search. Following screening of titles and abstracts, 339 citations were excluded and 36 potentially relevant reports from the electronic search were retrieved for full-text review. Seven potentially relevant publications were retrieved from the grey literature search for full-text review. Of these 43 potentially relevant articles, 36 publications were excluded for various reasons, and 7 publications met the inclusion criteria and were included in this report. These comprised 2 systematic reviews (SRs), 1 randomized controlled trial (RCT), 3 non-randomized studies, and 1 evidence-based guideline.

The included RCT was published in 2020 but was conducted between 2003 and 2005.[2] Although the authors stated that the dataset was previously unpublished, a subset of the same authors published results of an RCT conducted in 2005 within the same ED in Minneapolis, Minnesota. This study, Martel et al. (2005),[11] was identified by 1 of the 2 SRs included in this report.[6,11] The potential overlap of this evidence is therefore unclear.

Furthermore, 2 relevant retrospective observational studies were conducted at the same Minneapolis ED, overlapped chronologically, and included some of the same authors. Therefore, these 2 studies may include overlapping evidence. However, as suggested by patient numbers, patient inclusion criteria, and reported outcomes, these studies were not entirely overlapping (i.e., some unique patients were included); therefore, both are included in this report.[3,4] These retrospective observational studies did not overlap with the Martel et al. (2020) RCT.

Appendix 1 presents the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)[12] flow chart of the study selection. Appendix 5 presents the overlap of primary study evidence of the SRs included in this report.

Summary of Study Characteristics

Both SRs had broader inclusion criteria than the present review.[6,13] Specifically, both SRs included studies that examined any chemical restraint intervention in acute care settings.[6,13] Only the characteristics and results of the subset of relevant studies are described in this report.

Study Design

Two SRs were identified that fit the inclusion criteria presented in Table 1.[6,13] Muir-Cochrane et al. was published in 2020 and identified 23 RCTs, 8 study arms of which were relevant to this report.[6] Bak et al. was published in 2019 and identified 53 RCTs and 1 SR; 8 of these RCTs and the SR were relevant to this report.[13]

Four primary studies are included in this report: 1 RCT published in 2020[2] and 3 retrospective observational studies.[3,4,14]

One guideline with relevant recommendations was identified and included in this report.[7] Recommendations were formulated by the American Academy of Emergency Medicine (AAEM) using evidence collected by a systematic literature search of all study designs, using human subjects, and published in the English language. All relevant supporting evidence was assigned a quality category based upon study design and methodology, as well as a grade based upon study design and relevance to the research question. Quality categories ranged from outstanding (highest) to unsatisfactory (lowest), while grade categories ranged from Grade A (highest) to Grade F (lowest). Recommendations were assigned a class; however, it was not clear how these related to the assigned quality and grade categories.

Country of Origin

The included SRs originated in Australia[6] and the Netherlands.[13] All primary studies were conducted and authored in the US.[2-4,14] Two of the retrospective observational studies were conducted at the same ED in Minneapolis and had overlapping study time frames.[3,4] The identified guidelines were also from the US; however, the AAEM did not specify that the recommendations were intended to apply to American emergency physicians.[7]

Patient Population

The SR from Australia included adult patients with uncontrolled aggression, anxiety, or violent behaviour, or patients with mental health conditions who were non-consenting to treatment.[6] The SR from the Netherlands included adults with psychiatric disorders or intoxication encountered in the ED or mental health ward.[13]

The RCT (Martel et al. 2020)[2] enrolled adults older than 18 years requiring parenteral sedation for acute agitation. The study excluded patients who were prisoners, in police custody, pregnant, breastfeeding, had a relevant allergy, or were capable of providing consent but did not consent to treatment. The authors also stated that safety considerations may have impacted enrolment.[2]

Two of the retrospective observation studies included adult patients in the same ED that presented with alcohol intoxication and altered mental status.[3,4] Cole et al. also reported that a blood ethanol concentration greater than 80 mg/dL was required for patient inclusion.[3] The third retrospective observational study included patients who behaved in a manner that posed a threat to their own well-being and/or others, were combative, or had a head injury that required prehospital physical restraint. Included patients had a median age of 31 years.[14]

The guidelines focused on the safety aspects of droperidol administration to patients in the ED for any indication.[7]

Interventions and Comparators

The 2 SRs had a broad focus on chemical restraint of adults in acute care (including droperidol) and neither SR specified a comparator.[6,13] Muir-Cochrane et al. identified RCT evidence on IV and intramuscular (IM) droperidol doses of 5 mg and 10 mg.[6] Bak et al. identified RCT evidence on 4 mg, 5 mg, and 10 mg doses of droperidol without distinguishing between IM and IV administration routes. In the reporting of evidence, Bak et al. reported outcomes for each drug independently without the context of the comparator used in the individual RCTs.[13]

The RCT compared IM administration of 5 mg droperidol, 10 mg ziprasidone, 20 mg ziprasidone, and 2 mg lorazepam.[2]

Two retrospective observational studies with possible overlap of included patients compared droperidol, haloperidol, and olanzapine antipsychotic drugs.[3,4] The median doses for both studies were 5 mg droperidol, 5 mg haloperidol, or 10 mg olanzapine.[3,4] Macht et al. compared a median droperidol dose of 2.9 mg to a median haloperidol dose of 7.9 mg following an ED protocol change from droperidol to haloperidol.[14]

The guidelines considered the intervention of droperidol, including whether appropriate and safe use of IM- or IV-administrated doses of droperidol less than 2.5 mg required electrocardiogram (ECG) or telemetry monitoring, and the safety of IM droperidol doses of up to 10 mg.[7]

Outcomes

The SR by Muir-Cochrane et al. included studies that reported any measures of aggression, agitation, or violent behaviours, and results were reported narratively. The meta-analysis (MA) component of the SR reported the combined results of 2 RCTs for the following outcomes: median time to calm, proportion of patients calm at 5 minutes, and proportion of patients calm at 10 minutes. The MA also examined if there was a significant correlation between antipsychotic drug dose and frequency of adverse events.[6] Relevant outcomes in the SR by Bak et al. were proportion of patients experiencing adverse events, oversedation, EPS, acute dystonia, akathisia, hypotension or hypertension, and QTc elongation (> 500 ms).

The RCT reported the following outcomes: proportion adequately sedated at 15 minutes, severity of agitation using the Altered Mental Status Scale (AMSS), severity of agitation using the Behavioural Activity Rating Scale (BARS), the proportion of patients requiring additional sedation during the entire encounter, the proportion of patients requiring additional sedation before adequate sedation, the time until additional sedatives were administered, the ED length of stay (LOS), hospital LOS, nasal end-tidal carbon dioxide ($ETCO_2$), peripheral oxygen saturation (SpO_2), and QTc interval.[2] The AMSS ranges from −4 to 4, with zero representing normal responsiveness, speech, facial expression, and no ptosis. On the AMSS scale, 4 represents an agitated patient with combative or violent responsiveness, loud outbursts of speech, agitated facial expressions, and no ptosis, while −4 represents an overly sedated patient who is unresponsive to mild prodding or shaking and has limited recognizable speech, marked relaxed facial expression with a slacked jaw, glazed eyes, and marked ptosis. Martel et al. did not report BARS outcomes but instead reported an analysis of the correlation between AMSS and BARS to demonstrate that observations were consistent.[2]

It is likely that Cole et al. and Klein et al. reported on an overlapping patient cohort; however, these studies focused on different outcomes.[3,4] Cole et al. focused on ED LOS.[3] Klein et al.

also reported on ED LOS, but additionally reported the proportion of patients that required rescue sedation within 1 hour, the proportion of patients that required rescue sedation over the entire encounter, and adverse events that included the proportion of patients requiring intubation, experiencing torsades de points, cardiac arrest, akathisia, dystonia, anaphylaxis, and rash.[4]

Macht et al. reported on the proportion of patients requiring rescue sedation within 1 hour, QTc interval, adverse events including cardiac arrest and hypotension (SpO_2 < 90 mm Hg), and events requiring intubation, bag mask ventilation, or administration of anti-dysrhythmic medication.[14]

The guidelines did not specify outcomes but reported a focus on therapeutic efficacy outcomes and outcomes related to ECG monitoring of patients administered droperidol.[7]

Summary of Critical Appraisal

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

Systematic Reviews

The 2 SRs included in this review had important strengths, including a comprehensive systematic literature search, a PRISMA flow chart describing the literature selection, data extraction methodology, an MA, a table of study characteristics, critical appraisal methodology, and a discussion on the limitations of the study.[6,13] Muir-Cochrane et al. contained additional unique strengths, including study selection that was conducted in duplicate, PICO (population, intervention, comparator, outcome)-formulated inclusion criteria, a statement of no potential conflicts of interest (COI), and an assessment of publication bias.[6] Bak et al. did not formulate a PICO research question but had clear inclusion and exclusion criteria.[13] The most important limitation of these SRs was a lack of critical appraisal reporting. Despite reporting an appropriate critical appraisal methodology for the included RCTs, appraisal results were not included in Bak et al. and were reported as a single numerical score in Muir-Cochrane et al. The potential bias in the body of evidence identified by these SRs was therefore unclear. The SR from Bak et al. lacked the unique strengths of Muir-Cochrane et al. and reported outcomes per study arm, removing information on the comparator used in the study, which may have removed important context. Muir-Cochrane et al. identified 2 RCTs relevant to the efficacy of droperidol that had suitable homogeneity for an MA. Bak et al. did not identify RCTs that reported the outcomes of interest on droperidol treatment for the MA, and reported only narratively on studies relevant to droperidol.[13] Therefore, both MAs of the included SRs were limited by the quantity of identified evidence.[6,13] The SR from Muir-Cochrane et al. reported limited comparative conclusions regarding the safety and dose of olanzapine compared to droperidol.[6] In the SR by Bak et al., it was unclear whether adverse events were not reported or whether no adverse events occurred for some included RCTs.[13]

RCT

One RCT was identified that was not included in the SRs.[2] This study had important methodological strengths including a CONSORT diagram of patient recruitment and enrolment, tabulated patient characteristics, sufficient randomization methodology, and appropriate statistical methods. The study clearly defined patient eligibility, interventions, and outcomes. Other strengths included sufficient power with no loss to follow-up, quantified adverse events, and a comprehensive discussion on the study's limitations. A statement

of no potential COIs was also provided. Although the study was published in 2020, it was conducted between 2003 and 2005, and the reporting delay may have introduced unknown bias. The delay was discussed in detail by the authors. The authors did not provide allocation concealment methodology, details regarding the role of blinded investigators, nor an analysis of potential confounders.

Non-Randomized Studies

Two of the identified retrospective observational studies, Cole et al. and Klein et al., may have reported different outcomes from a study with an overlapping patient cohort and therefore shared similar strengths and limitations regarding methodology.[3,4] Both publications provided a clear objective and clear patient criteria; used appropriate statistical methods; tabulated patient characteristics; used a blinded data extractor; and provided a comprehensive discussion on the limitations of the study. Only Cole et al. reported no potential COI and accounted for concomitant administration of diphenhydramine,[3] while only Klein et al. reported quantified adverse event data.[4] Due to the retrospective data, neither publication was able to account for IM versus IV administration; however, Cole et al. reported that IV administration represented less than 6% of patients.

The third retrospective observational study provided a clear objective, a statement of no potential COIs, appropriate statistical methodology, and a comprehensive discussion on study limitations. The study reported adverse events quantitatively and used a data extractor that was blinded to the study protocol. The study was limited by retrospective design and did not distinguish between IM and IV administration. The study was subject to a significant potential for selection bias in that limited patient characteristics were reported on a cohort with unclear selection criteria, limited data on concomitant medications was reported, significant loss to follow-up was observed, and incomplete data on outcomes of QTc were reported.

Guidelines

Guidelines from the AAEM provided a clear objective; however, the guidelines did not specifically describe a research question or the patient population of interest. A systematic literature search was used to identify relevant evidence. Significant limitations in the reported methodology included a lack of stakeholder involvement, lack of information on other treatment options, lack of advice and implications for implementation, and unclear potential COI. Importantly, although the quality of the supporting evidence was assessed, the criteria used lacked sufficient detail and were not used to describe the body of identified evidence. Additionally, the recommendations were assigned a class that was not defined or associated with the assessed quality or the assigned grade of the supporting evidence. However, the supporting evidence was associated with each clear and unambiguous recommendation.

Summary of Findings

Appendix 4 presents the main study findings and authors' conclusions.

Clinical Effectiveness and Safety of Droperidol

The 2 included SRs summarized the following body of evidence regarding the comparative safety and efficacy of droperidol for patients in acute care settings.[6,13] Muir-Cochrane et al. summarized 8 RCTs relevant to droperidol.[6] Two RCTs, both appraised as high-quality studies, enrolled an overlapping cohort of 361 patients and observed that IV administration of midazolam with droperidol was associated with a significantly greater number of successful sedations than IV droperidol or IV olanzapine alone. In contrast, another high-quality RCT

with 91 participants found that IM droperidol was quicker and safer than IM midazolam, and the combination of droperidol and midazolam administered intramuscularly offered no advantages. Another high-quality study including 144 randomized patients with acute agitation in the ED found that IM midazolam and IM droperidol were quicker and more effective than IM ziprasidone; however, patients treated with IM midazolam required more frequent rescue sedation and experienced more frequent respiratory distress. Another RCT randomized 336 patients to receive IV midazolam concomitantly with placebo, IV droperidol, or IV olanzapine. This RCT was also appraised as a high-quality study; it found that the addition of either droperidol or olanzapine decreased the time to adequate sedation. In an MA, Muir-Cochrane et al. included 2 of the RCTs above with sufficient homogeneity, and this combined dataset did not identify a statistically significant difference between droperidol and olanzapine in terms of the proportion of adequately sedated patients at 5 minutes or 10 minutes post-administration. This analysis also identified a statistically significant increase in adverse events with an increased dose of olanzapine from 5 mg to 10 mg but not with an increased dose of droperidol from 5 mg to 10 mg. The highest reported frequency of overall adverse events was reported as 16.2% with 10 mg droperidol. Although narrative conclusions from Muir-Cochrane et al. favoured the safety and efficacy of 5 mg olanzapine in quickly producing calm in distressing situations, no significant differences to 5 mg droperidol administration in safety or efficacy were identified in this SR. Limited conclusions specific to droperidol were reported.[6]

Additional findings summarized by Bak et al. (2019) included safety results of an RCT that compared droperidol and olanzapine and did not identify a statistically significant difference in the frequency of cardiovascular arrhythmia adverse events.[13] Bak et al. also included an MA from an SR that compared droperidol to haloperidol in 1 RCT of 228 patients in which no statistically significant difference in efficacy was identified.[13] The SR from Bak et al. presented evidence that supported the authors conclusions that olanzapine, haloperidol plus promethazine, and droperidol were the most effective and safe for rapid tranquilization in the ED. With regard to QTc, the evidence supported the author's conclusion that the prevalence of unsafe QTc following droperidol treatment is rare and comparable to other antipsychotic drugs. For some of the included RCTs in Bak et al., it was unclear whether adverse events were not reported or there were no adverse events.[13] The frequencies of adverse events following droperidol administration were variable between identified studies in the 2 included SRs and included events of hypotension,[6] respiratory depression,[6] acute dystonia,[6,13] airway obstruction,[6] hypotension,[6,13] arrhythmia,[6] bradycardia,[6] hypoventilation,[6] EPS,[13] akathisia,[13] oversedation,[6,13] and QT elongation.[13]

The RCT published in 2020 by Martel et al. compared 5 mg IM droperidol, 2 mg IM lorazepam, 10 mg IM ziprasidone, and 20 mg IM ziprasidone in a total of 115 randomized patients.[2] For the primary outcome of proportion of adequately sedated patients (AMSS ≤ 0) at 15 minutes, droperidol was statistically superior to the other treatments. For the other efficacy outcomes of requirement for additional sedative medications and ED LOS, no statistically significant differences between groups were identified. With regard to safety outcomes, statistically significant differences in $ETCO_2$ change and a composite outcome of $ETCO_2$ change and hypoxemia (SpO_2 < 90%) favoured droperidol. Despite favouring droperidol, this respiratory depression composite outcome was the most frequently observed adverse event observed in this report, reported in 12% of patients. No significant differences in QTc or other respiratory outcomes were identified.[2] The conclusions from the authors of the study support droperidol as being more effective than lorazepam or ziprasidone for the treatment of acute agitation in the ED while causing fewer respiratory depression episodes, and with a similar QTc.[2] Limited

patient characteristics were reported in Martel et al. (2020); therefore, these results are of unclear generalizability and potential risk factors for adverse events were not assessed.[2]

Two retrospective observational studies published in 2019 compared droperidol, olanzapine, and haloperidol administered to patients in the ED intoxication unit.[3,4] Cole et al. found that patients administered droperidol monotherapy for acute agitation secondary to alcohol intoxication had significantly shorter ED LOS than either comparator group.[3] Adverse event data were not reported in this study other than the authors observed no cases of sudden cardiac death.[3] Klein et al. observed a lower proportion of patients requiring rescue sedation who were treated with either droperidol or olanzapine compared with haloperidol in a similar patient population in the same setting.[4] No significant differences in adverse event frequency were observed in this cohort of more than 15,000 patients. The authors concluded that major adverse events were rare, but they did not examine potential risk factors.[4]

The oldest included study, a retrospective observational study from 2014, reported on the use of droperidol compared to haloperidol for prehospital physical restraint of 532 patients with threatening behaviour.[14] In this study, no statistically significant differences were observed in the proportion of patients requiring rescue sedation, QTc length, or adverse events. One patient treated with droperidol suffered cardiopulmonary arrest; however, the authors did not attribute this to torsades de pointes or droperidol administration.[14]

Guidelines

One set of guidelines from 2015 provided recommendations regarding droperidol administration by emergency physicians.[7] Three recommendations were formulated based upon both outstanding and good quality studies comprising Grade A and Grade B evidence. The recommendations were also assigned a class to reflect the strength of each recommendation; however, these classes were not defined in the publication. The AAEM assigned a Class B strength to the first recommendation that droperidol is an efficacious treatment of agitation, headache, and nausea. The guideline committee's second recommendation was that there is insufficient evidence to recommend mandating an ECG or telemetry monitoring for doses less than 2.5 mg given either intramuscularly or intravenously (Class A strength). A dose of less than 2.5 mg is considered off-label in the US, and the FDA black box warning does not apply to off-label dose levels.[7] The third recommendation was that IM doses of up to 10 mg of droperidol appear to be as safe and effective as other medications used for sedation of agitated patients (Class B). The authors also stated that it is well established that antipsychotic drugs increase QTc in a dose-related manner, but they did not make statements about ECG or telemetry monitoring of patients administered more than 2.5 mg droperidol. Furthermore, the authors encouraged a clarification of the US FDA black box warning to address the dose of droperidol with regard to the FDA recommendation.[7]

Limitations

The evidence identified and included in this report contain an unclear quantity of overlap (i.e., some of the same patients were included in more than 1 publication); therefore, some evidence may be disproportionally represented. The majority of the evidence identified in this report was from RCTs included in 2 SRs.[6,13] The critical appraisals conducted in the SRs were not reported in sufficient detail to assess potential bias concerns in this body of evidence. None of the identified studies reported detailed patient characteristics or analyzed the data for possible risk factors for the reported serious adverse events. Therefore, this evidence had unclear generalizability to all adult patients in acute care settings. The ethical issue of

informed consent for agitated patients in acute care in the evidence included in this report may have not been appropriately addressed. Furthermore, the recommendations identified in this report are limited by a lack of context as the authors did not define the classes assigned to grade the strength of recommendations.[7]

Conclusions and Implications for Decision- or Policy-Making

This report identifies and summarizes evidence on the use of droperidol for agitated, aggressive, and violent adult patients in acute care settings. This body of evidence consists of 2 SRs,[6,13] 1 RCT,[2] and 3 retrospective observational studies.[3,4,14] There is considerable overlap between the RCTs included in the SRs (outlined in Appendix 5). One set of guidelines was identified that included recommendations for emergency physicians regarding management of patients with droperidol.[7]

There was consistent evidence that no other tested antipsychotic drug (haloperidol, olanzapine, lorazepam, or ziprasidone) demonstrated superior sedative efficacy to droperidol.[2-4,6,13,14] Evidence for sedative efficacy of antipsychotic drugs for patients in acute care settings was from 2 RCTs, both with fewer than 50 patients in each study arm. Findings from these RCTs supported the superiority of droperidol over ziprasidone[2,6,11] and lorazepam.[2] Efficacy evidence of droperidol compared with olanzapine and haloperidol was mixed in 4 RCTs, either favouring droperidol or finding no significant difference.[6,13]

Potentially serious adverse events were identified in this evidence, including respiratory depression and QTc prolongation. One RCT reported statistically significant differences in adverse events favouring droperidol over lorazepam and ziprasidone in the frequency of respiratory depression events.[2] The remaining comparative evidence of adverse event profiles of antipsychotic drugs did not identify any additional statistically significant differences, including evidence from 3 retrospective observational studies, 2 of which had partially overlapping cohorts of more than 10,000 patients.[3,4] None of the identified studies examined potential correlations between the incidence of adverse events and patient risk factors, making the generalizability of the droperidol safety profile for all adult patients in acute care settings unclear. No identified studies had a primary outcome of safety; therefore, some studies may have been insufficiently powered to detect any differences between treatment arms.

Three evidence-based recommendations from the AAEM were formulated, one of which was relevant to patient monitoring.[7] This recommendation was based upon high-quality evidence and it stated that there is currently insufficient evidence to recommend mandating an ECG or telemetry monitoring of patients administered dose levels of droperidol less than 2.5 mg, either intravenously or intramuscularly. The authors also recommended that droperidol is as efficacious as other medications used for the treatment of agitation and that IM doses up to 10 mg are comparably safe.[7] No evidence was identified regarding implementation and/or potential challenges for the use of droperidol for sedating adult patients in acute care in the Canadian health care setting.

A black box warning regarding droperidol was issued by the FDA in 2001 based upon post-marketing surveillance.[3,7] This warning stated that ECG monitoring should be used

before administration of droperidol and that droperidol should not be administered if the QTc was longer than 440 ms in males or 450 ms in females.[7] None of the identified evidence provided patient baseline QTc or examined QTc as a potential risk factor before droperidol administration. Some study authors questioned the relevance of the evidence on which the black box warning was presumably based;[3,7] a future similarly powered study with a focus on examining serious adverse events and risk factors may provide the appropriate clarification.

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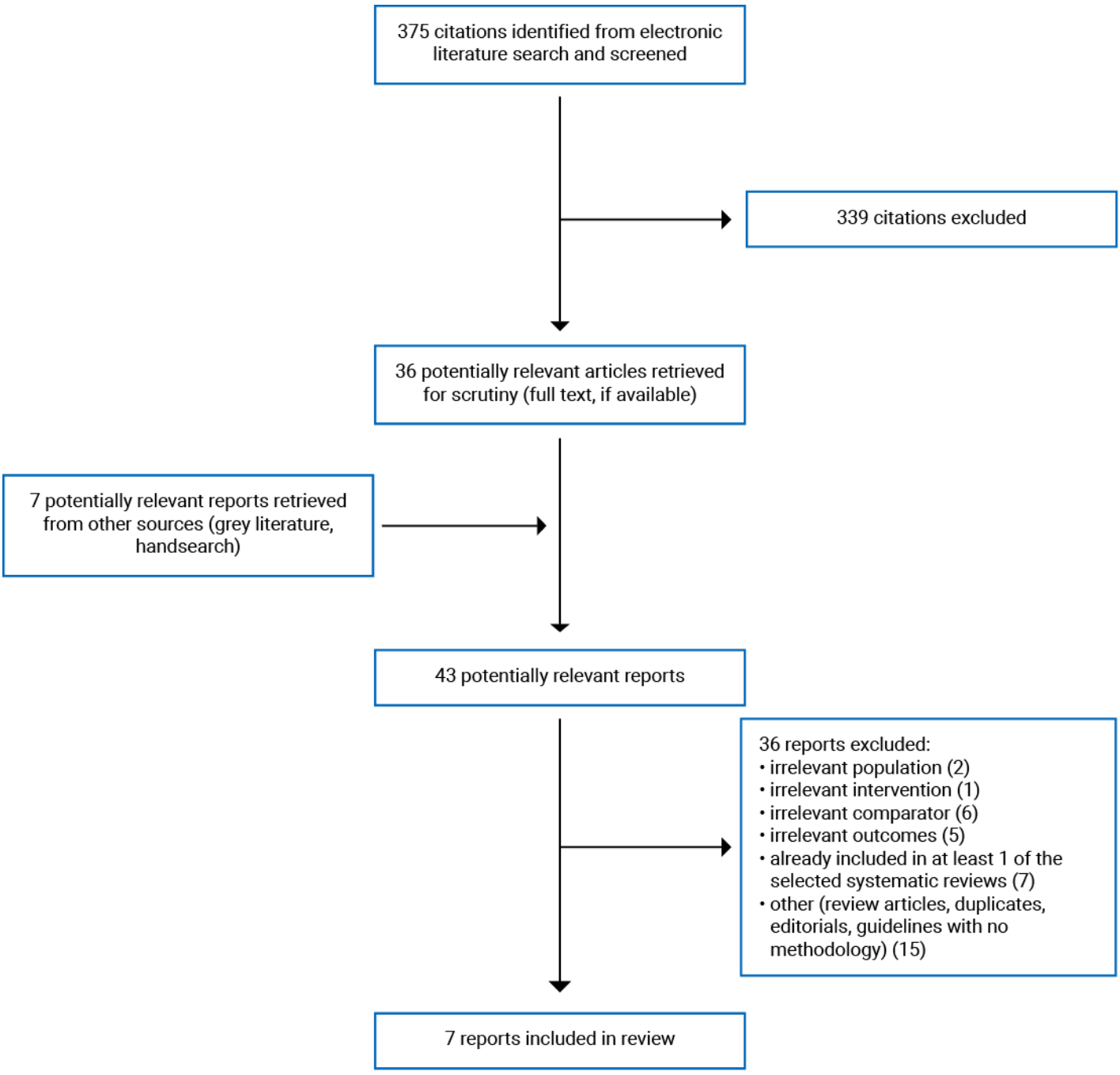
Appendix 1: Selection of Included Studies

Figure 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews

Study citation, country, funding source	Study designs and numbers of primary studies included	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Muir-Cochrane et al. (2020)[6] Australia Funding: No specific funding	23 RCTs with droperidol included in 8 RCTs	Adults with uncontrolled aggression, anxiety, violence, or with mental health conditions and non-consenting to treatment	Intervention: Chemical restraint (including droperidol) Comparator: Any reported	Outcomes: Any measure of aggression, agitation, or violent behaviours Follow-up: Any follow-up duration
Bak et al. (2019)[13] Netherlands Funding: No specific funding	53 RCTs and 1 SR with droperidol included in 8 of the RCTs and 1 SR	Adults with psychiatric disorder or intoxication, in the ED, ward in mental health hospital, or mixed Excluded patients with delirium	Intervention: Rapid tranquilization or pharmacological intervention (including droperidol)	Outcomes: • PANSS-EC • ACES • OASS Follow-up: At least 2 hours

ACES = Agitation-Calmness Evaluation Scale; ED = emergency department; OASS = Overt Agitation Severity Scale; PANSS-EC = Positive and Negative Symptom Scale-Excitement Components; RCT = randomized controlled trial; SR = systematic review.

Table 3: Characteristics of Included Primary Clinical Studies

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes
Randomized controlled trial				
Martel et al. (2020)[2] US Funding: Not reported	Adequately powered, randomized, double-blind, 4-arm trial (N = 115 patients)	Adults (≥ 18 years) requiring parenteral sedation for acute agitation Exclusions • Prisoners (or in police custody), pregnant or breastfeeding women, or those with a relevant allergy • Patients who were a risk to patient and staff safety • Patients who were able and did not provide informed consent	Interventions: • 5 mg IM droperidol • 10 mg IM ziprasidone • 20 mg IM ziprasidone • 2 mg IM lorazepam • Additional sedating medications as needed (recorded) in addition to standard ED care and monitoring	Outcomes: • AMSS • BARS • $ETCO_2$ • SpO_2 • QTc • Proportion adequately sedated at 15 minutes • Proportion requiring additional sedation during encounter and before adequate sedation • Time until additional sedation • ED LOS • Respiratory depression (SpO_2 < 90% or decreased $ETCO_2$ > 10 mm Hg or increased $ETCO_2$ > 15 mm Hg)
Non-randomized studies				

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes
Cole et al. (2019)[3] US Funding: Not reported	Retrospective observational cohort study, 3 arms (N = 11,787)	Adults (≥ 18 years) presenting to the ED intoxication unit with chief complaint of alcohol intoxication or altered mental status, and ethanol > 80 mg/dL in blood. Exclusions: multiple antipsychotic drugs administered	Interventions: • Droperidol (median dose 5 mg) • Haloperidol (median dose 5 mg) • Olanzapine (median dose 10 mg) Diphenhydramine was frequently administered concomitantly (droperidol 62%, olanzapine 13%, and haloperidol 87%)	Outcome: ED LOS
Klein et al. (2019)[4] US Funding: Not reported	Retrospective observational cohort study, 3 arms (N = 15,918)	Adults (≥ 18 years) presenting to the ED intoxication unit with chief complaint of altered mental status	Interventions: Initial antipsychotic drug • Droperidol (median dose 5 mg) • Haloperidol (median dose 5 mg) • Olanzapine (median dose 10 mg) Diphenhydramine was frequently administered concomitantly but the frequency was not reported	Outcomes: • Rescue sedation within 1 hour • Rescue sedation during encounter • ED LOS • Adverse events ◦ Intubation ◦ Torsades de pointes ◦ Cardiac arrest ◦ Akathisia ◦ Dystonia ◦ Anaphylaxis ◦ Rash

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes
Macht et al. (2014)[14] US Funding: AHRQ and NIH grants	Retrospective observational cohorts chronologically separated by ED protocol change from droperidol to haloperidol (N = 532)	Patients "behaving in a manner that poses a threat to their own well-being or others" or combative, head-injured patients requiring prehospital physical restraint Exclusions: Patients receiving droperidol as an antiemetic	Interventions: • Droperidol (median dose of 2.9 mg) • Haloperidol (median dose 7.9 mg)	Outcomes: • Rescue sedation within 30 minutes of arrival at ED • QTc • Adverse events ◦ SBP > 90 mm Hg ◦ Dysrhythmia ◦ Cardioversion or defibrillation ◦ Ventilation ◦ Intubation ◦ Cardiac arrest ◦ Mortality

AHRQ = Agency for Healthcare Research and Quality; AMSS = Altered Mental Status Scale; BARS = Behavioural Activity Rating Scale; ED = emergency department; $ETCO_2$ = end-tidal carbon dioxide; LOS = length of stay; NIH = National Institutes of Health; SBP = systolic blood pressure; QTc = QT interval; SpO_2 = peripheral oxygen saturation.

Table 4: Characteristics of Included Guideline

Intended users, target population	Intervention and practice considered	Major outcomes considered	Evidence collection, selection, and synthesis	Evidence quality assessment	Recommendation development and evaluation	Guideline validation
AAEM (2015)[7]						
Intended users: Emergency physicians Target population: ED patients receiving droperidol for any indication	Appropriate and safe use of droperidol for any management of patients in the ED	Efficacy, role of ECG monitoring, maximal dosing	Electronic search of droperidol and Inapsine (1995 to 2014), selection (all study designs) done in duplicate; synthesis was done by independent and joint review and discussion	Quality ranking assigned as outstanding, good, adequate, poor, or unsatisfactory based upon 2 criteria (design consideration and methodology consideration)	Evidence categorized as supportive, neutral, or opposed Quality and grade of evidence used to determine the level of recommendation	No methodology provided for internal or external review by experts or stakeholders

AAEM = American Academy of Emergency Medicine; ED = emergency department.

Appendix 3: Critical Appraisal of Included Publications

Table 5: Strengths and Limitations of Systematic Reviews and Meta-Analyses Using AMSTAR 2[8]

Strengths	Limitations
Muir-Cochrane et al. (2020)[6]	
• Comprehensive systematic literature search performed • Study selection performed in duplicate • PICO-formulated study questions and inclusion criteria used • PRISMA flow chart of literature selection presented • Data extraction methodology provided • Limited eligible studies to RCTs • Conducted an MA and combined results of comparable studies • A table of limited study characteristics provided • Critical appraisal using validated criteria conducted • Statement of no potential COI provided • Assessment of publication bias performed • Discussion of study limitations included	• No list of excluded studies provided • Few comparable studies identified for MA • Limited reporting of critical appraisal • Comparative conclusions were limited
Bak et al. (2019)[13]	
• Comprehensive systematic literature search performed • Clear inclusion and exclusion criteria used • PRISMA flow chart of literature selection presented • Data extraction methodology provided • Limited eligible studies to RCTs and SRs • Conducted an MA and combined results of comparable studies • A table of limited study characteristics provided • Critical appraisal using validated criteria conducted (for RCTs only) • Discussion of study limitations included	• No list of excluded studies provided • Study selection not performed in duplicate • Criteria for selection of SRs not included • No critical appraisal summary presented • Few comparable studies identified for MA • Statistical heterogeneity not reported • Reported results per study arm removing comparator context • Potential COI reported • No assessment of publication bias performed

AMSTAR 2 = A MeaSurement Tool to Assess systematic Reviews 2; COI = conflict of interest; CONSORT = Consolidated Standards of Reporting Trials; MA = meta-analysis; PICO = population, intervention, comparator, outcome; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT = randomized controlled trial; SR = systematic review.

Table 6: Strengths and Limitations of RCT Clinical Study Using the Downs and Black Checklist[9]

Strengths	Limitations
Martel et al. (2020)[2]	
• CONSORT diagram for patient recruitment/enrolment (supplementary material) presented • Patient characteristics tabulated • Randomization methodology described • Statistical methods described • Sample size determined a priori based on clinical significance (not based on primary outcome) • Clearly defined patient eligibility • Clearly defined intervention • Clearly defined outcomes and validated correlation of related outcomes • Comprehensive discussion on study limitations presented • Adverse events discussed and quantified • Statement of no potential COIs provided • No loss to follow-up	• Allocation concealment methodology not described • Unclear role of blinded investigators • Discontinuous study with protocol modifications — study completed in 2005, published in 2020 • Unclear if this study was previously published in 2005 • No analysis of potential confounding variables

Table 7: Strengths and Limitations of Non-Randomized Clinical Studies Using the Downs and Black Checklist[9]

Strengths	Limitations
Cole et al. (2019)[3]	
• Objective clearly stated • Patient inclusion and exclusion criteria described • Statistical methods provided • Tabulated patient characteristics • Clearly described outcomes and findings • Data extractor blinded to study protocol • Comprehensive discussion on study limitations included • Statement of no COI provided	• Retrospective observational unblinded study • Chronological bias in treatment groups • Unclear reasons for group assignment • No adverse event data • IM or IV administration not distinguished
Klein et al. (2019)[4]	
• Objective clearly stated • Patient inclusion and exclusion criteria described • Statistical methods provided • Tabulated patient characteristics • Clearly described outcomes and findings • Data extractor blinded to study protocol • Comprehensive discussion on study limitations included • Adverse event data discussed and quantified	• Retrospective observational unblinded study • Chronological bias in treatment groups • Unclear reasons for group assignment • No COI statement • IM or IV administration not distinguished
Macht et al. (2014)[14]	
• Objective clearly stated • Statistical methods provided • Data extractor blinded to study protocol • Adverse event data discussed and quantified • Statement of no COI provided • Comprehensive discussion on study limitations included	• Retrospective observational unblinded study • IM or IV administration not distinguished • Limited patient characteristics • Limited inclusion and exclusion criteria provided • Chronological bias in treatment groups • Limited data on concomitant medications • Large loss to follow-up and incomplete outcome data

Table 8: Strengths and Limitations of Guideline Using AGREE II[10]

Item	Assessment
AAEM (2015)[7]	
Domain 1: Scope and purpose	
1. The overall objective(s) of the guideline is (are) specifically described.	Yes
2. The health question(s) covered by the guideline is (are) specifically described.	No
3. The population (e.g., patients, public) to whom the guideline is meant to apply is specifically described.	Unclear
Domain 2: Stakeholder involvement	
4. The guideline development group includes individuals from all relevant professional groups.	No
5. The views and preferences of the target population (e.g., patients, public) have been sought.	No
6. The target users of the guideline are clearly defined.	Yes
Domain 3: Rigour of development	
7. Systematic methods were used to search for evidence.	Yes
8. The criteria for selecting the evidence are clearly described.	No
9. The strengths and limitations of the body of evidence are clearly described.	No
10. The methods for formulating the recommendations are clearly described.	No
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	Yes
12. There is an explicit link between the recommendations and the supporting evidence.	Yes
13. The guideline has been externally reviewed by experts before its publication.	No
14. A procedure for updating the guideline is provided.	No
Domain 4: Clarity of presentation	
15. The recommendations are specific and unambiguous.	Yes
16. The different options for management of the condition or health issue are clearly presented.	No
17. Key recommendations are easily identifiable.	Yes
Domain 5: Applicability	
18. The guideline describes facilitators and barriers to its application.	No
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	No
20. The potential resource implications of applying the recommendations have been considered.	No
21. The guideline presents monitoring and/or auditing criteria.	No
Domain 6: Editorial independence	
22. The views of the funding body have not influenced the content of the guideline.	Unclear
23. Competing interests of guideline development group members have been recorded and addressed.	No

AGREE II = Appraisal of Guidelines for Research and Evaluation II.

Appendix 4: Main Study Findings and Authors' Conclusions

Summary of Findings of Systematic Reviews

Muir-Cochrane et al. (2020)[6]

Main Study Findings

RCTs comparing droperidol to another antipsychotic drug

- Yap et al. (2017) (N = 92)
  - Quality: 13 out of 13
  - Midazolam-droperidol versus olanzapine or droperidol for methamphetamine-related acute agitation in the psychiatric intensive care unit (PICU)
  - IV midazolam-droperidol sedated significantly more patients than IV droperidol or IV olanzapine
- Taylor et al. (2017) (n = 361)
  - Quality: 13 out of 13
  - Midazolam-droperidol versus olanzapine or droperidol for acute agitation in PICU
  - IV midazolam-droperidol sedated significantly more patients than IV droperidol or IV olanzapine
- Calver et al. (2015) (N = 206)
  - Quality: 13 out of 13
  - IM droperidol versus IM haloperidol for sedation of PICU patients with aggressive behaviours
  - Similar sedative efficacy; haloperidol was safer
- Chan et al. (2013) (N = 336)
  - Quality: 13 out of 13
  - IV droperidol and IV olanzapine were both more effective as an adjunct to IV midazolam compared to IV midazolam alone at reducing time to adequate sedation in the ED
- Isbister (2017) (N = 91)
  - Quality: 13 out of 13
  - IM droperidol versus IM midazolam or IM midazolam-droperidol in the ED
  - IM droperidol was quicker and safer for sedation of violent and aggressive patients
  - The combination offered no additional benefit
- Knott et al. (2006) (N = 153)
  - Quality: 13 out of 13
  - IV midazolam versus IV droperidol of acutely agitated patients in the ED
  - Interventions were equally effective at sedation within 10 minutes
  - Midazolam was faster, but more patients required airway management and further sedation
- Martel et al. (2005) (N = 144)
  - Quality: 13 out of 13

- IM midazolam versus IM droperidol or IM ziprasidone of acutely agitated patients in the ED
- IM midazolam and IM droperidol were quicker and more effective than ziprasidone
- More patients treated with IM midazolam required rescue sedation treatments and experienced respiratory distress

Meta-analysis

Chan et al. (2013) and Taylor et al. (2017) had sufficient homogeneity for dosing, outcome measures, and time frames for meta-analysis (I^2 = 0%)

- Time to sedation
  - Median difference: 0.1 (95% CI, −0.115 to 0.254) minutes favouring droperidol over olanzapine (not significant)
  - No significant difference between olanzapine and droperidol in percentage of adequately sedated patients at 5 minutes or 10 minutes
- Adverse events (MA of Chan et al. and Taylor et al.), %
  - Droperidol 5 mg: 10.7%
  - Droperidol 10 mg: 16.2%
    - Difference between doses in frequency of adverse events was not significant (odds ratio [OR] = 0.6; 95% CI, 0.3 to 1.4)
  - Olanzapine 5 mg: 8.3%
  - Olanzapine 10 mg: 20%
    - Lower doses significantly decreased frequency of adverse events (OR = 0.4; 95% CI, 0.2 to 0.8)
  - Rate of adverse events between droperidol and olanzapine not statistically tested

Authors' Conclusion

"This study provides clear guidance than 5 mg olanzapine delivered intramuscularly is both safe and effective in quickly producing calm in potentially distressing situations, and that it is as effective, and safer, than higher doses (p. 14)."[6]

"…5 mgs olanzapine produced the lowest rate of adverse events. Thus, of the three drug choices 5 mg IM olanzapine was the most effective and safest [chemical restraint] option in the short-term (p. 14)."[6]

The above conclusions were based upon 1 RCT in which the authors of the study had concluded that the numbers of patients experiencing adverse events were similar between groups at a 5 mg dose: droperidol (12 of 112; 10.7%) and olanzapine (9 of 109; 8.3%).

Bak et al. (2019)[13]

Main Study Findings

SR of Khokhar and Rathbone (2016)

- Efficacy
  - Droperidol versus haloperidol (1 RCT; Cocchi et al. [1971], n = 228): relative risk (RR) = 1.01 (95% CI, 0.93 to 1.09)

    - Droperidol versus midazolam (1 RCT; Knott et al. [2006], n = 153): RR = 0.96 (95% CI, 0.72 to 1.28)
    - Droperidol versus olanzapine (1 RCT; Chan et al. [2013], n = 221): RR = 1.02 (95% CI, 0.94 to 1.11)
- Cardiovascular arrhythmia
    - Droperidol versus olanzapine (1 RCT; Chan et al. [2013], n = 221): RR = 0.32 (95% CI, 0.01 to 7.88)

Data from RCTs (not direct comparator studies)

- Antipsychotic drugs (IM): Percentage (or range of percentages across different studies) of patients reaching calmness
    - Within 15 to 20 minutes
        - Droperidol: 53% to 92%
        - Haloperidol: 67% to 91%
        - IV Droperidol + midazolam: 89%
        - IV Olanzapine: 66%
    - Within 2 hours
        - Droperidol: 98%
        - Droperidol + midazolam: 96%
        - Haloperidol: 60% to 89%
        - Haloperidol + promethazine: 89% to 97%
        - Aripiprazole: 60% to 84%
        - Olanzapine: 73% to 91%
        - Ziprasidone: 29% to 90%
        - Loxapine: 66% to 74%
        - Placebo: 28% to 44%
- Antipsychotic drugs (IM): Mean time (or range of percentages across different studies) to calmness (minutes)
    - Droperidol: 8 to 25
    - Droperidol + midazolam: 25
    - Lorazepam: 48
    - Haloperidol: 30
    - Haloperidol + promethazine: 20 to 30
    - Midazolam: 20 to 24
    - Haloperidol + lorazepam: 44
    - Haloperidol + midazolam: 10
    - Olanzapine: 30
    - Olanzapine (IV): 11
    - Risperidone + lorazepam: 43
- Adverse events (not direct comparator studies; for some RCTs it was unclear whether adverse events were not reported or there were no adverse events to report)
    - Oversedation

        - Droperidol: 1%
        - Lorazepam: 10%
        - Haloperidol: 0% to 36%
        - Haloperidol + promethazine: 3%
        - Haloperidol + midazolam: 40%
        - Aripiprazole: 4% to 9%
        - Olanzapine: 3% to 13%
        - Risperidone: 13%
        - Risperidone + lorazepam: 13%
        - Levomepromazine: 8%
        - Ziprasidone: 10%
        - Loxapine: 11% to 13%
        - Placebo: 2% to 10%
    - Movement disorders
        - EPS
            - Haloperidol: 6% to 55%
            - Haloperidol + promethazine: 0% to 74%
            - Haloperidol + lorazepam: 5%
            - Haloperidol + midazolam: 44%
            - Aripiprazole: 2%
            - Olanzapine: 0% to 5%
            - Risperidone: 6% to 8%
            - Ziprasidone: 0% to 52%
            - Placebo: 2% to 7%
        - Acute dystonia
            - Droperidol: 0% to 1%
            - Haloperidol: 0% to 17%
            - Haloperidol + lorazepam: 3%
            - Haloperidol + midazolam: 10%
            - Aripiprazole: 1% to 2%
            - Olanzapine: 0% to 4%
            - Haloperidol + promethazine: 0%
            - Risperidone: 2%
        - Akathisia
            - Haloperidol: 4% to 46%
            - Aripiprazole: 3%
            - Olanzapine: 3%
            - Levomepromazine: 8%
    - Hypotension or hypertension:
        - Droperidol: 0% to 4%

        - Droperidol + midazolam: 2% to 42%
        - Midazolam: 5%
        - Haloperidol: 0% to 17%
        - Haloperidol + lorazepam: 3%
        - Haloperidol + promethazine: 10%
        - Haloperidol + midazolam: 10%
        - Olanzapine: 0% to 4%
        - Levomepromazine (hypotension): 16%
        - Levomepromazine (hypertension): 3%
    - Cardiovascular adverse effects: QT elongation > 500 ms:
        - Droperidol: 1% to 6%
        - Droperidol + midazolam: 1% to 14%
        - Haloperidol: 0% to 6%
        - Aripiprazole: 0% to 6%
        - Olanzapine: 0% to 3%
        - Placebo: 0% to 8%

Authors' Conclusion

"Droperidol has been abandoned for some years because of QT-time prolongation. However, recent studies have shown that the prevalence of exceeding unsafe QT-times is rare and not more than with other antipsychotics… The problem of QT elongation in droperidol appears a rather smaller problem and not more prevalent compared to other antipsychotics (p. 96)."[13]

"At an ED the context asks for a more rapid onset of calmness and medical safety equipment is at hand allowing midazolam, droperidol or droperidol plus midazolam IV or IM to be used, medications that reaches calmness very fast but also need medical attention (p. 98)."[13]

"Olanzapine, haloperidol plus promethazine, or droperidol are most effective and safe for use as rapid tranquilisation. Midazolam sedates most quickly. But due to increased saturation problems, midazolam is restricted to use within an emergency department of a general hospital (p. 78)."[13]

Summary of Findings of Included RCT Primary Clinical Studies

Martel et al. (2020)[2]

Main Study Findings

- Difference in proportion adequately sedated at 15 minutes (95% CI):
    - Droperidol versus lorazepam: 33% (8% to 58%)
    - Droperidol versus ziprasidone (10 mg): 39% (14% to 64%)
    - Droperidol versus ziprasidone (20 mg): 29% (3% to 54%)
- Difference in reduction in median AMSS at 15 minutes (95% CI):
    - Droperidol versus lorazepam: 2 (0 to 3)
    - Droperidol versus ziprasidone (10 mg): 1 (0 to 2)
    - Droperidol versus ziprasidone (20 mg): 1 (0 to 2)

    - BARS outcomes were reported with a Spearman rank correlation coefficient for AMSS of 0.95 ($P < 0.001$).
- Additional sedatives required
    - Entire encounter:
        - Droperidol: 20%
        - Ziprasidone (10 mg): 25%
        - Ziprasidone (20 mg): 16%
        - Lorazepam: 39%
    - Before adequate sedation:
        - Droperidol: 8%
        - Ziprasidone (10 mg): 14%
        - Ziprasidone (20 mg): 13%
        - Lorazepam: 23%
    - Time until additional sedatives (minutes), median (IQR):
        - Droperidol: 90 (32 to 149)
        - Ziprasidone (10 mg): 46 (30 to 60)
        - Ziprasidone (20 mg): 38 (34 to 40)
        - Lorazepam: 60 (49 to 78)
- LOS in ED, median (IQR)
    - Time from administration to discharge (minutes):
        - Droperidol: 341 (235 to 400)
        - Ziprasidone (10 mg): 285 (236 to 383)
        - Ziprasidone (20 mg): 325 (257 to 412)
        - Lorazepam: 379 (199 to 524)
    - Total time in ED (minutes):
        - Droperidol: 563 (477 to 615)
        - Ziprasidone (10 mg): 540 (438 to 720)
        - Ziprasidone (20 mg): 551 (455 to 640)
        - Lorazepam: 611 (439 to 782)
- Adverse events
    - Respiratory outcomes
        - Hypoxemia (SpO_2 < 90%):
            - Droperidol: 8%
            - Ziprasidone (10 mg): 7%
            - Ziprasidone (20 mg): 19%
            - Lorazepam: 23%
        - Change in $ETCO_2$ (decreased > 10 mm Hg, or increased > 15 mm Hg):
            - Droperidol: 8%
            - Ziprasidone (10 mg): 32%
            - Ziprasidone (20 mg): 32%

        - Lorazepam: 45%
        - P = 0.03
    - Respiratory depression (hypoxemia or change in $ETCO_2$ composite):
        - Droperidol: 12%
        - Ziprasidone (10 mg): 36%
        - Ziprasidone (20 mg): 39%
        - Lorazepam: 48%
        - P = 0.04
  - QT elongation (QTc), median (IQR):
    - Droperidol: 413 (389 to 452)
    - Ziprasidone (10 mg): 410 (385 to 432)
    - Ziprasidone (20 mg): 428 (391 to 459)
    - Lorazepam: 414 (380 to 429)

Authors' Conclusion

"Droperidol was more effective than lorazepam or either dose of ziprasidone for the treatment of acute agitation in the ED and caused fewer episodes of respiratory depression (p. 1)."[2]

"QTc durations were similar in all groups (p. 1)."[2]

"Droperidol also tended to have higher AMSS scores (less sedation) once adequate sedation was achieved, suggesting that earlier reevaluation may be more feasible with droperidol than lorazepam or ziprasidone (Figure 2). This has obvious benefits in patients requiring psychiatric evaluation and on total time patients spend in the ED who require medications for agitation management. We found no difference in effectiveness or safety between lorazepam and ziprasidone. Our data align with subsequent in the intervening years demonstrating IM droperidol to be a safe, effective first-line agent for acute agitation in the ED (p. 7)."[2]

Summary of Findings of Included Non-Randomized Primary Clinical Studies

Cole et al. (2019)[3]

Main Study Findings

- Entire cohort: ED LOS (minutes), mean (95% CI):
  - Droperidol (n = 3,790): 499 (493 to 506)
  - Haloperidol (n = 1,449): 524 (515 to 537)
  - Olanzapine (n = 6,549): 533 (528 to 539)
- Cohort not administered concomitant anticholinergic agents: ED LOS (minutes), mean (95% CI):
  - Droperidol (n = 1,537): 468 (454 to 478)
  - Haloperidol (n = 204): 506 (488 to 551)
  - Olanzapine (n = 6,145): 530 (524 to 536)

Authors' Conclusion

"Droperidol, when given as monotherapy for sedation of acute agitation secondary to alcohol intoxication, was associated with significantly shorter ED length of stay than either parenteral

haloperidol or olanzapine. Despite olanzapine's longer half-life, no difference in ED length of stay was observed between haloperidol or olanzapine (p. 83)."[3]

"No cases of sudden cardiac death occurred (p. 79)."[3]

Klein et al. (2019)[4]

Main Study Findings

- Percentage difference requiring rescue sedation (within 1 hour) (95% CI):
  - Droperidol versus olanzapine: 0% (−1% to 1%)
  - Droperidol versus haloperidol: −7% (−9% to −5%)
  - Olanzapine versus haloperidol: −7% (−9% to −5%)
  - Negative percentage indicates first drug had fewer patients requiring rescue sedation
- Percentage difference requiring rescue sedation (entire ED encounter) (95% CI):
  - Droperidol versus olanzapine: −2% (−3% to 0%)
  - Droperidol versus haloperidol: −9% (−11% to −7%)
  - Olanzapine versus haloperidol: −7% (−9% to −5%)
  - Negative percentage indicates first drug had fewer patients requiring rescue sedation
- ED LOS (minutes), median (IQR) (entire cohort):
  - Droperidol (n = 4,947): 511 (393 to 647)
  - Haloperidol (n = 2,146): 537 (410 to 672)
  - Olanzapine (n = 8,825): 544 (418 to 690)
- Adverse events, % (95% CI):
  - Intubation:
    - Droperidol (n = 4,947): 0.2% (0.1% to 0.3%)
    - Haloperidol (n = 2,146): 0.2% (0.1% to 0.5%)
    - Olanzapine (n = 8,825): 0.4% (0.2% to 0.6%)
  - Torsades de points: 0%
  - Cardiac arrest:
    - Droperidol (n = 4,947): 0%
    - Haloperidol (n = 2,146): 0%
    - Olanzapine (n = 8,825): 0.01% (0.01% to 0.06%)
  - Akathisia:
    - Droperidol (n = 4,947): 0.1% (0.03% to 0.2%)
    - Haloperidol (n = 2,146): 0%
    - Olanzapine (n = 8,825): 0.02% (0% to 0.1%)
  - Dystonia:
    - Droperidol (n = 4,947): 0.04% (0% to 0.1%)
    - Haloperidol (n = 2,146): 0.05% (0% to 0.3%)
    - Olanzapine (n = 8,825): 0.02% (0% to 0.1%)
  - Anaphylaxis: 0%
  - Rash:

- Droperidol (n = 4,947): 0%
- Haloperidol (n = 2,146): 0%
- Olanzapine (n = 8,825): 0.02% (0% to 0.1%)

Authors' Conclusion

"At 1 h, droperidol and olanzapine resulted in the lowest rates of rescue medication administration (11% for each) compared with haloperidol (18%). Adverse events were relatively uncommon. Our findings support that olanzapine and droperidol may be more effective than haloperidol for achieving adequate sedation in agitated patients (p. 488)."[4]

"Although this study was not necessarily powered to detect adverse events, we reviewed over 15,000 cases of antipsychotic administration and found that serious adverse events were rare (p. 487)."[4]

"There were no significant differences in major adverse events (p. 484)."[4]

"Diphenhydramine was given more often [than benzodiazepines] (87% of haloperidol cases, 13% of olanzapine cases, and 62% of droperidol cases)...we may have missed cases of EPS because we used diphenhydramine administration as a surrogate to search for EPS. It is also possible that EPS rates are underestimated due to the frequent co-administration of diphenhydramine, especially with droperidol and haloperidol (p. 488)."[4]

Macht et al. (2014)[14]

Main Study Findings

- Difference in percentage of patients requiring rescue sedation (within 1 hour) (95% CI):
  - Droperidol versus haloperidol: −2.9% (−8.5% to 2.6%)
  - Droperidol had fewer patients requiring rescue sedation
- QTc difference (ms), median (95% CI):
  - Droperidol versus haloperidol: 5 (−10 to 6)
  - Droperidol had greater median QTc
- Droperidol versus haloperidol: difference in percentage of patients with the following QTc intervals (95% CI)
  - QTc 450 to 474 ms: 6% (−6% to 19%)
  - QTc 475 to 499 ms: 5% (−4% to 14%)
  - QTc > 500 ms: 1% (−6% to 4%)
  - Droperidol had more patients within each elongation interval
- Adverse events: no significant differences
  - Intubation:
    - Droperidol (n = 218): 2%
    - Haloperidol (n = 314): 4%
  - Cardiac arrest:
    - Droperidol (n = 218): 0.4%
    - Haloperidol (n = 314): 0%
  - SpO_2 < 90 mm Hg:
    - Droperidol (n = 218): 3%

        - Haloperidol (n = 314): 4%
    - Anti-arrhythmic:
        - Droperidol (n = 218): 0.5%
        - Haloperidol (n = 314): 2%
    - Bag mask ventilation:
        - Droperidol (n = 218): 2%
        - Haloperidol (n = 314): 4%

Authors' Conclusion

"Our study did not demonstrate a statistically significant difference between droperidol and haloperidol in effectiveness, measured by use of further medications within 30 minutes of ED arrival (p. 6)."[14]

"Our findings suggest that droperidol does not have a worse side-effect profile than haloperidol. We do, however, recognize that a patient in the droperidol group suffered cardiopulmonary arrest. This patient had history of congenital heart disease and a median sternotomy scar from a surgery at age 3, and did not require defibrillation or anti-dysrhythmic drugs for resuscitation, suggesting that torsades de pointes was a less-likely cause of his cardiopulmonary arrest (p. 6)."[14]

"In this cohort of agitated patients treated with haloperidol or droperidol in the prehospital setting, there was no significant difference in QTc prolongation, adverse events, or need for repeat sedation between haloperidol and droperidol. There was a trend toward fewer adverse events and less need for repeat sedation in the droperidol group. Further study with larger patient groups is needed to better define the safest and most effective method to sedate agitated patients in the prehospital setting (p. 8)."[14]

Summary of Recommendations of Included Guideline

AAEM (2015)[7]

Recommendations and Supporting Evidence

"Droperidol is an efficacious treatment of agitation, headache, and nausea (p. 93)." - Class B (outstanding and good quality studies of Grade A and Grade B)

"There is currently insufficient evidence to recommend for mandating an electrocardiogram (ECG) or telemetry monitoring for doses < 2.5 mg given either i.m. or i.v. (p. 96)." - Class A (outstanding and good quality studies of Grade A and Grade B)

"Intramuscular doses of up to 10 mg of droperidol appear to be as safe and as effective as other medications used for sedation of agitated patients (p. 96)." - Class B (outstanding and good quality studies of Grade A and Grade B)

Quality of Evidence and Strength of Recommendations

- Grade of evidence
    - Grade A: Randomized clinical trials or meta-analyses (multiple clinical trials) or randomized clinical trials (smaller trials) directly addressing the review issue
    - Grade B: Randomized clinical trials or meta-analyses (multiple clinical trials) or randomized clinical trials (smaller trials) indirectly addressing the review issue

    - Grade C: Prospective, controlled, non-randomized, cohort studies
    - Grade D: Retrospective, non-randomized, cohort, or case-control studies
    - Grade E: Case series, animal/model scientific investigations, theoretical analyses, or case reports
    - Grade F: Rational conjecture, extrapolations, unreferenced opinion in literature, or common practice
- Quality of evidence
    - Outstanding: Design and methodology both with appropriate considerations
    - Good: Design or methodology with appropriate considerations
    - Adequate: Design with possible bias and adequate methodological consideration
    - Poor: Limited design or methodological considerations
    - Unsatisfactory: Questionable design or methodological considerations

Appendix 5: Overlap Between Included Systematic Reviews

Table 9: Overlap in Relevant Studies Between Systematic Reviews

Study citation	Muir-Cochrane et al. (2020)[6]	Bak et al. (2019)[13]
Calver et al. (2013)[15]	No	Yes
Calver and Isbister (2014)[16]	No	Yes
Calver et al. (2015)[5]	Yes	Yes[a]
Chan et al. (2013)[1]	Yes	No[a]
Cocchi et al. (1971)[17]	No	No[a]
Hick et al. (2001)[18]	No	Yes
Isbister et al. (2010)[19]	No	Yes
Isbister (2017)[20]	Yes	No
Khokhar and Rathbone (2016)[21a]	No	Yes
Knott et al. (2006)[22]	Yes	Yes[a]
Martel et al. (2005)[11]	Yes	No
Resnick and Burton (1984)[23]	No	No[a]
Richards et al. (1998)[24]	No	Yes
Rosen et al. (1997)[25]	Yes	No
Taylor et al. (2017)[26]	Yes	Yes
Van Leeuwen et al. (1977)[27]	No	No[a]
Yap et al. (2017)[28]	Yes	No

[a]Khokhar and Rathbone (2016) is itself a systematic review included in Bak et al. (2019); reference is also included in Khokar and Rathbone.